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Brief Reviews
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Beyond Good and Evil: Molecular Mechanisms of Type I and III IFN Functions

Jack W. Dowling*,† and Adriana Forero†

IFNs are comprised of three families of cytokines that confer protection against pathogen infection and uncontrolled cellular proliferation. The broad role IFNs play in innate and adaptive immune regulation has placed them under heavy scrutiny to position them as "friend" or "foe" across pathologies. Genetic lesions in genes involving IFN synthesis and signaling underscore the disparate outcomes of aberrant IFN signaling. Abrogation of the response leads to susceptibility to microbial infections whereas unabated IFN induction underlies a variety of inflammatory diseases and tumor immune evasion. Type I and III IFNs have overlapping roles in antiviral protection, yet the mechanisms by which they are induced and promote the expression of IFN-stimulated genes and inflammation can distinguish their biological functions. In this review, we examine the molecular factors that shape the shared and distinct roles of type I and III IFNs in immunity. ***The Journal of Immunology*****, 2022, 208: 247–256.**

Interferons are broad class II cytokines induced by recognition of pathogen-associated molecular patterns and stress stimuli such as DNA damage, organelle stress, and damage-associated molecular patterns (DAMPs). IFNs carry out pleiotropic effects through the induction of IFN-stimulated genes (ISGs), which control cellular proliferation, metabolism, Ag presentation, cell recruitment and activation, and inflammation. Across decades of studies, IFNs have irrefutably been deemed essential in the interference against viral infections across tissues, a property that has earned them their name (1). It is now understood that IFNs play a protective role in the pathogenesis of bacterial, fungal, and parasitic infections (2–6), although in certain contexts, their expression can worsen infectious outcomes (7, 8). IFNs are also crucial effectors of anti-tumor immunity (9–12), not only because they inhibit cell proliferation and regulate metabolic function, but also by eliciting anti-tumor immune cell responses. However, the aberrant induction of IFNs has also been associated with loss of host fitness and resistance to antitumor immunity (13, 14), and it is thought to underlie the pathology of various inborn and acquired autoinflammatory (15, 16) and autoimmune diseases (17).

IFNs are classified into three families (types) and various subtypes on the basis of their stability at low pH (18). The human type I IFNs (IFN-α/β) are 17 predominantly acid-stable ligands that signal through the heterodimeric type I IFN receptor (IFNAR1 and IFNAR2) (19–21). The sole type II IFN, IFN-γ, is acid labile and engages the type II IFN receptor (IFNGR1 and IFNGR2) (22, 23). The type III IFNs (IFN-λ) are also acid labile and comprise four subtypes in humans (IFN-λ1–IFN-γ4). In contrast, the murine IFN-λ (mIfnλ) locus encodes functional IFN-λ2 and IFN-λ3 genes that share a very high degree of identity to the corresponding human genes. Unlike the intronless type I IFNs, type III IFNs genes contain introns. A premature stop codon in exon 1 and the loss of exon 2 of *mIfnλ1* render it a pseudogene (14). IFN-λs signal through a heterodimeric receptor composed of IFNLR1 and IL-10R2, with the later receptor subunit shared across the IL-10 family cytokines (24–26).

IFNs are further distinguished by the cells that secrete them. IFN-γ is secreted by leukocytes (18) and has a pivotal role in controlling microbial infections and conferring anti-tumor immunity (reviewed in Refs. 27, 28). In contrast, IFN-α/β and IFN-λ are broadly synthesized across cells types following the engagement of pattern recognition receptors (PRRs) and the activation of transcription factors (TFs), including IFN regulatory factors (IRFs) and NF-κB (29, 30). Signal transduction downstream of the IFN-α/β and IFN-λ receptors relies on JAKs (JAK1, TYK2, JAK2) to phosphorylate STAT1 and STAT2. Activated STATs bind to IRF9, forming the heterotrimeric ISGF3 transcriptional complex necessary for transduction of IFN stimulation response element–dependent ISGs. These similarities in signal transduction of IFNs led to early inferences on the redundancy of IFN-α/β and IFN-λ in antiviral protection. A growing body of work has now challenged this notion, demonstrating that IFN-α/β and IFN-λ coordinate unique biological functions. These distinct functions can be specified by the nature and dose of the stimulating ligand

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Abbreviations used in this article: AE, adverse effect; BBB, blood–brain barrier; BLIMP-1, B lymphocyte–induced maturation protein-1; DAMP, damage-associated molecular pattern; HBV, hepatitis B virus; HCV, hepatitis C virus; IAV, influenza virus A; IRF, IFN regulatory factor; ISG, IFN-stimulated gene; MAVS, mitochondrial antiviral signaling protein; MOI, multiplicity of infection; PRDI, positive regulatory domain I; PRR, pattern recognition receptor; ROS, reactive oxygen species; TF, transcription factor; ZEB1, zinc finger E-box–binding homeobox 1.

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(31–34) and the subcellular localization of PRR signaling complexes (35), which result in the induction of distinct IFN subtypes. Additionally, the identity of the infected or IFN-sensing cell can also further diversify the functions of IFNs (36).

The distribution of cognate IFN receptors is a major mechanism that defines IFN function. Although the type I IFN receptor is expressed ubiquitously across cells, the expression of IFNLR1 is most abundant in epithelial cells (37). Thus, IFN-λs have been firmly established as the stalwarts of antiviral protection in mammalian mucosal tissues, the liver (reviewed in Ref. 38), the placenta, and the blood–brain barrier (BBB) (reviewed in Ref. 6). IFN-α/β and IFN-λ also appear to elicit differential inflammatory responses. IFN-α/β elicits robust inflammatory responses while these responses are muted following IFN-λ sensing. This discrepancy is predominantly conserved in pulmonary and gastrointestinal epithelial cells and human hepatocytes (39–41). Moreover, IFN-λ protects mucosal barriers from excessive inflammation through signaling in epithelial (42) and immune cells (31, 43). However, in a subset of autoimmune diseases, IFN-λ can exacerbate skin pathologies (44–46). IFN-λ can also disrupt tissue repair during pulmonary hyperinflammatory conditions (47). Thus, the compartmentalization of IFN-mediated functions that is driven by tissue identity can be further shaped by the immunological context in which IFNs are induced. Emerging work also implicates IFN-λ in the regulation of immune cell function (3, 48–50) defining the innate and adaptive immune response to viral challenge. The consequences of IFN-λ signaling in these contexts are distinct from those elicited by IFN-α/β (3, 48, 51), making this an exciting area of future investigation of the crucial roles of IFNs in health and disease (Fig. 1).

Disruption in the tight regulation of IFN synthesis and IFN receptor signaling can result in inefficient or unabated IFN responses with deleterious consequences to the host. In this review, we explore the known factors that contribute to the distinct biological roles of type I and III IFNs and focus on our current understanding of 1) the nuanced regulation of IFN gene expression, 2) the divergent signal transduction cascades elicited by IFNs, and 3) the biological consequences of IFN induction across tissue types. Taken together, these observations highlight an evolutionary pressure to distribute antimicrobial innate and adaptive immune functions across these two cytokine families. Our understanding of the regulation of cytokine production and cytokine response is critical to exploit these responses for the management of both viral and non-viral diseases.

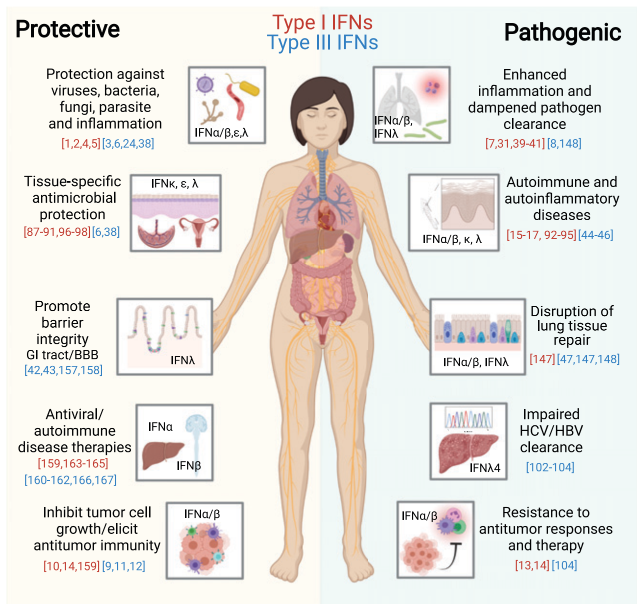

FIGURE 1. Consequences of IFN induction in health and disease. Type I and III IFNs can confer innate immune protection against various pathogens, including viruses, bacteria, fungi, and parasites. A subset of IFNs are expressed in a tissue-specific manner and thus elicit protection at these sites. Beyond preventing pathogen dissemination, tissue-specific or tissue-biased IFNs can protect mucosal barriers such as the skin, placenta, and female reproductive tract, or by supporting barrier integrity as observed in the gastrointestinal (GI) tract and BBB. IFN-based therapies are being used to treat chronic viral infections, autoimmune disease, and cancer (left). Unrestricted IFN production can promote inflammatory responses and impair microbial clearance. By eliciting inflammation, IFNs can disrupt epithelial cell functions and tissue repair and circumvent the antitumor immune response. Single-nucleotide polymorphism in the IFN-λ4 locus lead to a loss of response to IFN therapy and impaired viral clearance (right). Relevant studies for the specific roles of type I IFN (red) and type III IFN (blue) in health and disease are indicated.

Regulation of type I and III IFN gene expression

The expression of type I and III IFN genes is distinctly regulated following pathogen-associated molecular pattern recognition (29) (Fig. 2, left). Sendai virus infection of human-derived myeloid cell lines at distinct multiplicities of infection (MOIs) results in the differential induction of IFN-α/β subtypes (52). PRR activation induced IFN-β and IFN-α1, 2, and 8 in an MOI-independent manner. In contrast, a subset of IFN-α genes were only induced at low MOI (IFN-α4, 6, 7, 10, and 17), whereas a second subset of IFN-α genes appeared to be most flexible. These genes (IFN-α5, 14, 16, and 21) were readily responsive to PRR activation at a high MOI, and at a low MOI their upregulation was dependent on IFNAR signaling (52). Whether MOI affects the kinetics of transactivation of distinct IFN-λ genes is less clear. However, in vivo studies show that viral concentration plays a role in determining whether IFN-λ or IFN-α/β dominates the antiviral response. In low-dose infections with influenza virus A (IAV), IFN-λ responses protect murine lungs. At high infectious doses, IFN-α/β is elicited and drives neutrophil infiltration and inflammatory tissue damage (31). Interestingly, the IFN-λ predominance following epithelial infections appears to be conserved across RNA viruses such as IAV (31, 32), human rotavirus (33), reovirus (53), hepatitis E virus (34), and enteroviruses (36, 54). The bias in IFN-λ secretion and the elevated expression of IFNLR1 in these tissues position IFN-λ as local elicitors of antiviral protection. IFN-α/β responses would then be required upon uncontrolled viral replication and pathogen escape from primary sites of infection.

The molecular determinants that stipulate distinct IFN gene transactivation are the engagement of unique PRRs (55, 56), their subcellular localization (57), and the organelles from which PRR adaptors form signalosomes (35, 58) (Fig. 2, left). For example, sensing of DNA by Ku70 activates STING to preferentially induce *IFNλ1* expression (59, 60). TLR4 activates inflammation via TIRAP-MyD88 or TRAM- TRIF (Toll/IL-1R domain–containing adapter inducing IFN-β) adaptor proteins. Association of TLR4 with TIRAP-MyD88

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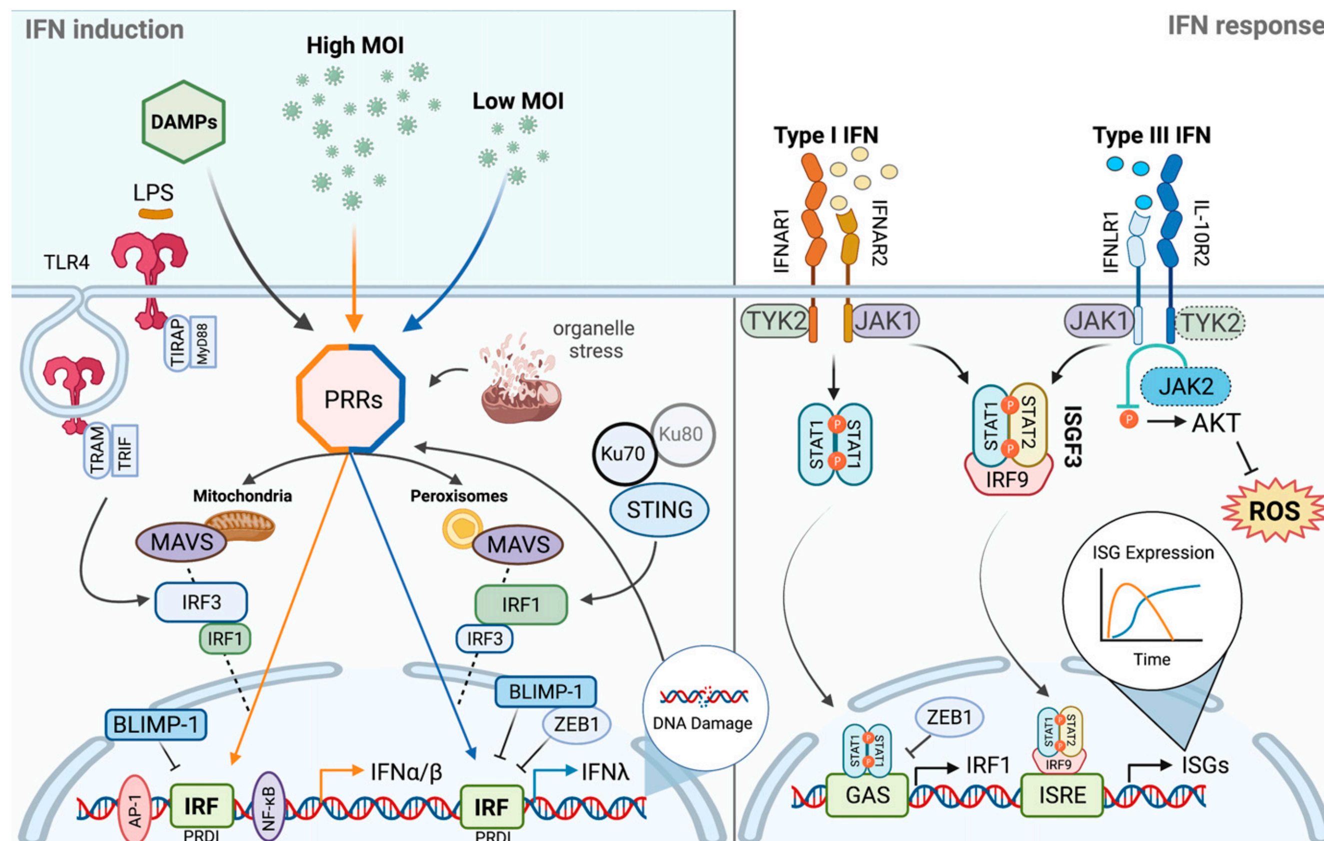

FIGURE 2. Regulatory mechanisms of IFN induction and signaling. Type I and III IFNs are induced upon pattern recognition activation (PRRs) by viral nucleic acids, DNA damage, organelle stress, and released DAMPs. The subcellular localization of PRRs and their adaptor molecules can activate distinct IRFs to bias IFN gene transactivation as denoted by the dashed lines. IRF recruitment to the PRDI elements in IFN promoters can be inhibited by negative transcriptional regulators such as BLIMP-1 and ZEB1 (left). Type I and III IFNs signal through cognate receptors that engage distinct JAKs and discrete downstream signaling cascades. This leads to STAT1-dependent induction of IRF1 through γ-activated sequence (GAS) binding and downstream proinflammatory genes, the ISGF3-dependent induction of IFN-stimulated response element (ISRE)–regulated ISGs, and the JAK2-AKT–mediated inhibition of ROS (right).

at the plasma membrane activates NF-κB. As TLR4 is endocytosed, it signals through TRAM-TRIF to activate IRF3. IRF3 activation results in *IFNB1* mRNA expression in response to TLR4 ligation (57). Similarly, the subcellular localization of adaptor proteins can impact the IFN response after PRR activation. Mitochondrial-localized mitochondrial antiviral signaling protein (MAVS) elicited more robust IFN production relative to cells expressing peroxisomal-localized MAVS in a virus-dependent manner (35). However, differences in the detection of *IFNλ1* mRNA over *IFNB1* mRNA was most pronounced in cells with peroxisomal-localized MAVS. A second study suggested that MAVS localization did not skew IFN induction or its anti–hepatitis C virus (HCV) efficacy (58). Limitations in the ability to accurately quantify IFN gene expression and protein production could account for these discrepancies. The breakdown of central tolerance (61) in *AIRE*-deficient individuals (62, 63) leads to the development of IFN-α/β and IFN-λ1 neutralizing Abs that enhance viral infectious disease severity (64, 65). Therefore, understanding the intricacies of how PRR ligands shape the cellular dependency on distinct receptor usage and adaptor localization to elicit differential IFN expression is of great significance. This understanding would guide the rational design of nucleic acid sensor agonists to bias IFN responses for the management of infectious diseases (66) and proliferative malignancies (67–69).

Transcriptional and epigenetic regulation of IFN expression

The patterns of IFN induction are dictated by the activation of distinct TFs that bind to defined regulatory sequences in the IFN gene promoters. The predominant IFN regulatory TFs are the IRFs, such as IRF3. Characterization of the *IFNB1* enhanceosome revealed that NF-κB and the AP-1 transcriptional complex synergize with IRF3 to induce the expression of *IFNB1* mRNA. In most cell types, the expression of IRF7 is induced upon IFN sensing (70). Although IRF7 synergizes with IRF3 to further promote the expression *IFNB1* (71), IRF7 is primarily necessary for the positive regulation of IFN-α genes. This property is imparted by the distinct affinities of IRF3 and IRF7 for defined promoter regulatory sequences in these genes (71–73). Thus, the expression of most of the IFN-α genes follows that of *IFNB1*. As observed for IFN-α/β, the timing and specificity of IRF activation can specify the timing of IFN-λ gene expression. IFN-λ gene expression is also regulated by both IRFs (IRF1, IRF3, and IRF7) and NF-κB (60, 74–76). The upstream promoter regulatory regions of *IFNλ2/3* are largely conserved, differing from each other by 5 nt. As such, it is thought that *IFNλ2/3* are coregulated by the same TFs. In contrast, the promoter sequence of *IFNλ1* is far less conserved. *IFNλ1* transcription can be elicited by IRF3 and IRF7, whereas the transactivation of *IFNλ2/3* appears to be driven primarily by IRF7 (77). Whether virus infections or other stress stimuli elicit unique signals to activate other

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coregulators of IFN gene expression (78) that can control the kinetics of IFN-α/β and IFN-λ gene expression remains to be explored in further depth.

Chromatin architecture and epigenetic regulation provide additional layers of transcriptional control (79). The transcriptional repressor B lymphocyte–induced maturation protein-1 [BLIMP-1 (PRDM1)] was among the first known inhibitors of *IFNB1* expression (80). BLIMP-1 binds to the positive regulatory domain I (PRDI) sequence of the *IFNB1* enhanceosome and prevents the recruitment of IRFs. Sequence analysis of the human *IFNλ1* promoter region identified PRDI sequences targeted by BLIMP-1 to inhibit *IFNλ1* expression in human airway and colon epithelial cells (76, 81). Similarly, loss of BLIMP-1 expression leads to an increase in *IFNλ2/3* expression in murine mammary epithelial cells (76, 82). The *IFNλ1* promoter was also shown to encode an E-box response element. The transcriptional repressor zinc finger E-box–binding homeobox 1 (ZEB1) bound to the *IFNλ1* promoter and inhibited *IFNλ1* expression (76). ZEB1 did not appear to regulate the expression of *IFNB1* mRNA following treatment with the synthetic dsRNA ligand, poly(I:C). This finding was among the first to suggest a targeted mechanism for subverting the induction of an IFN-λ response. However, ZEB1 can also indirectly silence type I and III IFN signaling in diseased epithelia. During severe asthmatic disease, injury of the airway epithelium elicits TGF-β–dependent responses to promote repair of the mucosal barrier. TGF-β induces the epigenetic reprogramming of epithelial cells, leading to increases in ZEB1 expression (83). Heightened ZEB1 expression muted the accumulation of IRF1, a positive regulator of type I and III IFN gene expression (84, 85), after poly(I:C) treatment. The loss of IRF1 expression impaired antiviral responses in cells that have undergone epithelial–mesenchymal transition, making them more susceptible to respiratory syncytial virus and rhinovirus infections. Therefore, heightened ZEB1 expression could account for the imbalance in IFN responses that worsen asthmatic and allergic disease and render individuals more susceptible to viral respiratory infections (reviewed in Ref. 86). Interestingly, it is suggested that the biased induction of *IFNλ1* downstream of peroxisomal-MAVS signaling is due to greater IRF1 induction (35). Whether this corresponds to a differential displacement of ZEB1 from *IRF1* and/or *IFNλ1* promoters remains to be addressed.

Tissue and species-specific IFN responses

IFN genes can also be expressed in a tissue- and species-specific manner, and their expression does not solely rely on IRF/NF-κB regulation. IFN-κ is a type I IFN that is constitutively expressed in keratinocytes and is necessary for the protection against viral pathogens such as HSV-1 (87) and human papillomavirus (88). Although viral infection or IFN stimulation can enhance the expression of *IFNκ* (89), the exact mechanisms that control IFN-κ expression are poorly understood. Distal TGF-β and p63-responsive enhancers and MAPK signaling cascades appear to be necessary for *IFNκ* regulation (90, 91). Elevated *IFNκ* expression has been associated with various skin manifestations of autoimmune disorders, such as dermatomyositis (92), systemic and cutaneous lupus erythematosus (93), and psoriasis (94). IFN-κ could promote inflammatory responses observed in patients by inducing ISG expression (95) and promoting secretion of the proinflammatory cytokine, IL-6. Another nonconventional type I IFN, IFN-ε, is expressed constitutively in the female reproductive tract (96) where it confers protection against viral and bacterial challenge. Unlike conventional IFNs, IFN-ε does not respond to PRR activation, suggesting that it is not controlled by IRF/NF-κB. Rather, IFN-ε expression is controlled by sex hormones. IFN-ε is induced by estrogens and repressed by progesterone, resulting in its dynamic expression throughout the estrous cycle (97, 98).

IFN genes can also be expressed in a species-specific manner. Humans and non-human primates encode the *IFNλ4* pseudogene (99). A duplication of *IFNλ1* and *IFNλ2* followed by head-to-head reintegration of this fragment into the genome gave rise to *IFNλ3* and *IFNλ4*. While IFN-λ1–IFN-λ3 share a high degree of homology, increased mutations in the IFN-λ4 gene made it a non-functional gene, poorly responsive to viral stimulation (100, 101). A single-nucleotide polymorphism can restore *IFNL4* expression (102) and correlates with impaired clearance of HCV and increased cancer susceptibility. Although the molecular mechanisms by which polymorphisms in *IFNL4* impact immune responses are not clear, the irrefutable health impact of genetic variance in *IFNL4* has been summarized in recent reviews (103, 104). Likewise, the expression of IFN-ω is species restricted. While its secretion has been detected from human, feline, and swine leukocytes, among other mammals, neither canines nor mice express IFN-ω. IFN-ω autoantibodies have been detected in autoimmune polyglandular syndrome type 1 patients (105) and individuals with severe COVID-19 (64). However, the role of IFN-ω in these pathologies is poorly understood. Findings of biased induction of IRFs by subcellular PRR/adaptor localization (35, 57), kinetic IFN regulation during infection, and tissue and species specificity of IFN subtypes (97) demonstrate the advantages of complementing the use of convenient and robust animal models with clinical specimens and human cellular models.

Receptor-mediated responses to type I and III IFNs

Cytokine-mediated signal transduction cascades are shaped by the strength and duration of the ligand-receptor interactions, the abundance of cell surface receptors, and the availability of adaptor molecules and transcriptional regulators across different cell types (Fig. 2, right). Extensive studies of type I IFN regulation have provided foundational knowledge on how each of these processes determines differential biological outcomes for IFN-α/β. The binding affinities of IFN-α/β for both the high-affinity (IFNAR2) and low-affinity (IFNAR1) receptors (21, 106, 107) dictate their antiviral and anti-proliferative properties. Mutagenesis studies demonstrate that the pleiotropic effects of IFNs (antiviral versus antiproliferative) can be uncoupled on the basis of their affinity for receptor subunits (108, 109). These mutations stabilize the ternary complex formed by ligand/receptor (110) and do not correlate with the downstream activation of STAT1. Therefore, these two biological functions could be dependent on either differential STAT2 activation, changes in the formation of transcriptional complexes, or other STAT-independent signal transduction cascades that can contribute to diversifying the functions of IFN-α/β. Similar differences in potency are observed across IFN-λ (IFN-λ3 > IFN-λ1 > IFN-λ2) (111). Ligand-targeted mutagenesis of IFN-λ3 enhances its affinity for IFNLR1 shifting the

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kinetics of ISG induction and antiviral protection in response to cytokine stimulation (108). These changes in IFN-λ3 receptor affinity did not affect the antiproliferative responses of IFN-λ.

The abundance of IFN-λ receptors at the cell surface play a critical role in dictating biological function. The kinetics and magnitude of ISG expression can be altered by not only by receptor affinity changes (108), but also through differences in the surface expression of IFN-λ receptors (40, 112). Receptor abundance can dictate the formation of distinct transcriptional complexes ISGF3 and/or STAT1 homodimers ($STAT1_2$) that distinguish the proinflammatory functions of IFN-α/β and IFN-λ signaling (40). Although robust induction of $STAT1_2$ occurs shortly after IFN-β stimulation, its induction is insufficient to drive downstream gene expression in IFN-λ3–treated human hepatocytes (40). $STAT1_2$ binds to γ-activated sequence elements in the promoters of IFN-responsive genes such as IRF1, a transactivator of proinflammatory chemokine genes. Therefore, IFN-α/β have a bias toward the induction of IRF1 and the expression of chemokines such as CXCL9, CXCL10, and CXCL11 (40, 113). Increasing IFNLR1 abundance in epithelial cells was sufficient to enhance IRF1 and chemokine expression. Although enhancing the affinity for IFNLR1 did not impact the antiproliferative properties of IFN-λ, exogenous IFNLR1 overexpression drastically enhanced its ability to inhibit cell growth (108). This is in line with the aforementioned changes in ISG subset expression upon IFNLR1 overexpression (40) and IFN-α/β receptor expression (114). Whether the enhanced antiproliferative responses observed upon IFNLR1 overexpression is due to increased IRF1 induction, a potent tumor suppressor gene (115), remains to be determined.

The mechanisms that differentially regulate IFN receptor signaling (116) and expression across cell types remain an open area of investigation. For example, cellular polarization and three-dimensional structure can increase the sensitivity to IFN-λ (40, 117). Epigenetic mechanisms can silence *IFNLR1* expression in transformed cells (118, 119). Lastly, viral infection and inflammatory stimulus differentially impact *IFNLR1* expression across cell types (40, 48). Whereas infection of murine bone marrow–derived dendritic cells with IAV elicits *Ifnlr1* mRNA expression (48), IAV does not induce significant changes in infected murine lungs or human epithelial cells (40). *IFNLR1* mRNA expression was also refractory to other viral and inflammatory challenge in epithelial cells. A better understanding of the regulation of IFN-λ receptor expression and stability will elucidate the specification of function of IFNs across disease states.

The role of JAKs in type I and III IFN signaling. IFN receptor signaling is mediated by the JAKs (JAK1, TYK2, JAK2), nonreceptor tyrosine kinases with broad functions in type I and II cytokine signaling (reviewed in Refs. 120, 121). Their central requirement in IFN signaling has been elucidated through in vitro studies, animal models, and patient-derived data. These studies have revealed the specific interactions between IFN receptor subunits and distinct JAKs, and they distinguished the requirements for JAK expression and its kinase activity. JAKs mediate the tyrosine phosphorylation of receptor chains, facilitate the docking of STATs and their C-terminal tyrosine phosphorylation, and stabilize cytokine receptors at the plasma membrane (122). JAK1 is a broad regulator of class II cytokine signaling, essential for the response to growth factors and immune regulatory cytokines. *Jak1* deficiency results in developmental abnormalities and perinatal lethality in mice (123). JAK1 interacts with the high-affinity receptors IFNAR2 and IFNLR1 and is indispensable for type I and III IFN responses (124–126). Inhibition of JAK1 kinase activity strongly inhibits ISG expression upon IFN-λ stimulation (127). An individual with a *JAK1* biallelic mutation associated with lowered JAK1 protein expression had diminished responses to IFN-α treatment and increased propensity to recurrent mycobacterial infections and early onset metastatic bladder carcinoma (128). Microsatellite instability can also result in the accumulation of JAK1 loss of function. Hyperactivating mutations in JAK1 have also been associated with myeloproliferative and lymphoproliferative diseases and autoimmune skin diseases (129). Leukemia-associated somatic JAK1 activating mutations are associated with a poor response to therapy and disease prognosis and result in the hyperresponsiveness to type I IFNs (130). However, whether the aberrant IFN-α/β or IFN-λ contribution to exacerbated inflammatory responses and deregulation of cell growth can be exploited for anti-cancer therapies remains to be determined.

Although the essential role of JAK1 in IFN-α/β and IFN-λ signaling is uncontested, the requirement for TYK2 in the response to both IFN families is less clear. TYK2 is activated in response signaling by cytokines including IL-6, IL-10, IL-12, and IL-23. A naturally occurring TYK2 mutation is associated with increased susceptibility to microbial infection, hyper-IgE syndrome, pneumonias, and abnormal skin disease (131). This patient had a frameshift mutation causing a premature stop codon and loss of TYK2 expression. IFN-α/β stimulation of patient-derived cells failed to promote JAK1, STAT1, STAT2, and STAT3 phosphorylation, a phenotype that can be recapitulated in $Tyk2^{-/-}$ mice (132). In vitro work demonstrated that TYK2 is necessary to respond to IFN-α/β stimulation (133, 134), acting as a scaffold for IFNAR1 as well as preventing endocytic recycling and premature degradation (122). Similarly, in vivo TYK2 deficiency leads to reduced IFNAR1 surface levels in humans (131), but less so in mice (135). TYK2-deficient individuals also displayed impaired, but not entirely abolished, IFN-α/β responses (136). The $Tyk2^{-/-}$ murine model demonstrated that impaired IFN-α/β responsiveness was dose-dependent, with increasing concentrations of IFN-α eliciting robust antiviral responses (135). Both clinical- and murine-derived data suggested that beyond impacting IFN responses, *Tyk2* loss severely impaired IL-12–mediated NK and T cell functions (135, 136). These results are in line with studies harnessing selective JAK inhibitors that demonstrate that TYK2 activity is predominantly required for IL-12, and to a lesser extent IFN-α, IL-6, or IL-10 cytokines (137).

As TYK2 stabilizes IL-10R2 expression and was proposed to be activated by IL-10 signaling (138), its involvement in IFN-λ signaling has been interrogated (136). TYK2-null patient-derived cells are partially impaired in their response to either IFN-λ or IL-10 stimulation (136). Animal studies demonstrate that *Tyk2* loss renders the host susceptible to IAV infection due to impaired ISG induction (127). However, it appears that IFN-λ does not heavily depend on TYK2 for signaling to the same extent as it is required for IFN-α/β signaling. Whereas intranasal treatment of $Tyk2^{-/-}$ mice with the recombinant type I IFN hybrid, IFN-$\alpha_{B/D}$ (139), could only partially elicit antiviral protection, IFN-λ2 protected mice from IAV disease and mortality. Interestingly, this study also suggested that the IFN-λ signaling requirement for TYK2 could vary across cell

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types, with signaling in neutrophils being more dependent on *TYK2* than are epithelial cells. These observations suggested that other JAKs could be required for IFN-λ signaling. JAK2 has been suggested to mediate canonical and non-canonical responses to IFN-λ stimulation (35, 43, 127). Future work will reveal the mechanism by which JAK2 regulates IFNLR1/IL-10R2 signaling and the impact that disease-driving JAK2 gain-of-function mutations (140) could have on the pathogenic potential of IFN-λ. It also remains to be determined how differences in the expression levels of IFN receptor subunits, the integration of other JAK/STAT-dependent signals, or independent signals across cells types dictate the need for specific JAKs in IFN signaling. This will broaden our understanding of the specific cascades that regulate antiviral or antiproliferative effector genes and guide the use of specific JAK inhibitors (120, 141) in the management of viral and inflammatory IFN-mediated diseases.

Unique functions of type I and III IFNs

The previously mentioned mechanisms can control the kinetics and magnitude of IFN synthesis and IFN signaling. These mechanisms can contribute to the diversification of biological functions that are controlled by either type I or III IFNs. Both cytokine families can drive the expression of ISGs with unique kinetics (142). IFN-α/β stimulation promotes a rapid burst of ISG expression, whereas IFN-λ induces a slower, sustained ISG response. These differences can be attributed to the temporal regulation of the ISGF3 complex and its potential recruitment to target promoters (40). In contrast, regulation of chromatin structure and TF promoter recruitment can impact differential ISG induction by IFN-α/β (143–146). Advanced tools with increased resolution to probe chromatin architecture as well as transcriptional and protein expression/modifications will permit us to build on the foundation of our current understanding to address their overlap in regulating IFN-α/β and IFN-λ responses.

Intriguingly, IFN-λ fails to elicit robust inflammation in the liver, lungs, and gut, whereas it can readily induce inflammatory responses in the skin epithelium. Whether this is due to increased IFNLR1 abundance, increased basal IRF1 expression, or other molecular determinants remains to be investigated. However, this underlies the importance of addressing how other cytokines and other stress stimuli (DNA damage, virus infection, DAMPs) coregulate IFN-λ responses to enhance its inflammatory potential. Pulmonary inflammatory responses elicited by poly(I:C) result in the breakdown of the epithelial barrier and concomitant induction of IFN-λ secretion from dendritic cells. Ablation of *Ifnlr1* improved epithelial cell repair both after poly(I:C) treatment and IAV infection (47, 147). Similarly, in a *Klebsiella pneumoniae* infection model, loss of *Ifnlr1* protected mice from exacerbated neutrophil transmigration and bacterial pneumonia (148). Advances in cell culture models (36, 40, 149, 150) and the development of robust animal models (31, 151–154) have furthered our understanding of the dynamics of IFN secretion (47) and the spatial response to IFN stimulation within a tissue (42). Such tools will be critical to address how the tissue identity and the context in which IFN responses are induced affect IFN signaling outcomes.

Lastly, IFNs differ in their ability to carry out non-canonical STAT-independent functions. In dextran sulfate sodium–induced colitis models, IFN-λ can dampen inflammation via inhibition of neutrophil production of reactive oxygen species (ROS) in a JAK2-AKT–dependent manner (43). Similarly, IFN-λ stimulation of neutrophils prevents neutrophil extracellular trap formation in a thromboinflammatory model (155). This is in contrast to the STAT-dependent protective functions that IFN-λ exerts on neutrophils to limit viral (31) and fungal (3) pulmonary infections, thereby preventing excessive inflammation from uncontrolled pathogen replication. The dual functions of IFN-λ in the regulation of neutrophil responses have been reviewed with greater detail (156). IFN-λ also protects against viral neuroinvasion during West Nile virus infection (157). Whereas IFN-β appeared to predominantly prevent viral replication, IFN-λ did not inhibit viral replication in keratinocytes or dendritic cells. Paradoxically, *Ifnlr1*$^{-/-}$ mice exhibited greater West Nile virus neuroinvasion due to loss of IFN-λ–dependent tightening of the BBB. Interestingly, whereas both IFN-β and IFN-λ3 treatment could elicit barrier tightening, the loss of STAT1 did not greatly impact IFN-λ–specific activities. Whether the non-canonical STAT-independent pathways that enforce endothelial barrier integrity control IFN-λ–mediated epithelial barrier reinforcement (158) is not known. It also remains to be determined whether that signal cascade overlaps with that which dampens neutrophil ROS production.

Conclusions

The antiviral and antiproliferative properties of IFNs have led to their clinical use to manage HCV, hepatitis B virus (HBV), hepatitis δ virus, and cancer (159). However, prolonged IFN-α treatment leads to treatment-limiting adverse effects (AEs). Thus, the tissue-restricted expression of IFNLR1 sparked interest in the alternate use of IFN-λ to treat chronic hepatic infections [HCV (160), HBV (161, 162)]. In HCV patients, IFN-λ drove a higher sustained virologic response and elicited fewer AEs than were observed in the IFN-α arm (160). IFN-λ treatment also resulted in a greater early decrease of HBV DNA and quantitative hepatitis B surface Ag. Upon treatment completion, both IFN arms showed comparable endpoint virologic outcomes and no significant differences in AEs. Posttreatment outcomes, such as the development of hepatitis B e Ag Abs (hepatitis B e Ag seroconversion), favored IFN-α therapy (161). IFN-β is used to treat multiple sclerosis, a progressive neurodegenerative disease, reducing the rate of multiple sclerosis relapses and disease progression with minimal AEs (163). Type I and III IFN therapies are now being assessed for the management of COVID-19. Nebulized IFN-β treatment increased the odds of clinical improvement (164), with s.c. delivery being more efficacious than i.v. delivery (165). Subcutaneous delivery of IFN-λ in non-critical COVID-19 patients (166, 167) was also well tolerated and provided indications that IFN-λ treatment could promote faster viral decline.

PRR agonists are being harnessed to elicit both antiviral and antitumor responses (66–68, 168). Knowledge of the determinants of IFN induction could inform strategies to bias the induction of specific IFN species. Such approaches could be beneficial in treating IFN signaling deficiencies in individuals with neutralizing IFN autoantibodies (62, 64, 105). Host–pathogen interactions can also disarm the IFN response or promote signaling pathways that exacerbate IFN-mediated damage. These interactions could

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alter the therapeutic window of IFNs, as could be the case for COVID-19 (169, 170). Age and biological sex can also play a significant role in the induction of innate immune responses, susceptibility to infections, the risk for autoimmune diseases, and the response to immunotherapies (171–173). Thus, exploring the multifaceted mechanisms that regulate the IFN response will facilitate the development of tailored IFN-based therapeutic interventions for treatment of a multitude of infectious and non-infectious diseases.

Disclosures

The authors have no financial conflicts of interest.

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Adriana Forero, Ph.D.

Institutional history

- Assistant Professor, The Ohio State University, 2020–present
- Post-doctoral Fellow, University of Washington (Dept. of Immunology), 2016–2020
- Post-doctoral Fellow, University of Washington (Dept. of Microbiology), 2014–2016
- Ph.D., University of Pittsburgh, 2008–2014

Research interests

- Cytokine regulation
- Signal transduction
- Innate immunity
- Host–pathogen interactions

I was born and raised in Barranquilla, Colombia, where a wide socioeconomic gap makes a large population disproportionately vulnerable to infectious diseases. This experience has driven my passion for the study of innate immune regulation and the host–pathogen interactions that shape the outcomes of viral disease. I migrated to the United States a month after my 17th birthday to pursue a degree in biology. I felt a sense of "otherness" based on my immigrant status and sexual identity. At such a young age, numerous microaggressions and more overt incidents eroded my confidence and distracted me from academic engagement. It was through the support of numerous mentors and sponsors that I found the strength to persevere. These mentors came in the form of strong, confident women at Wesleyan College as well as faculty and postdoctoral fellows at the University of Pittsburgh and the University of Washington. Their support was instrumental to navigating new environments and focusing on working toward my professional and scientific development. I now make concerted efforts to create and implement strategies to mitigate the distractions and barriers I faced to promote the growth and success of my trainees.

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